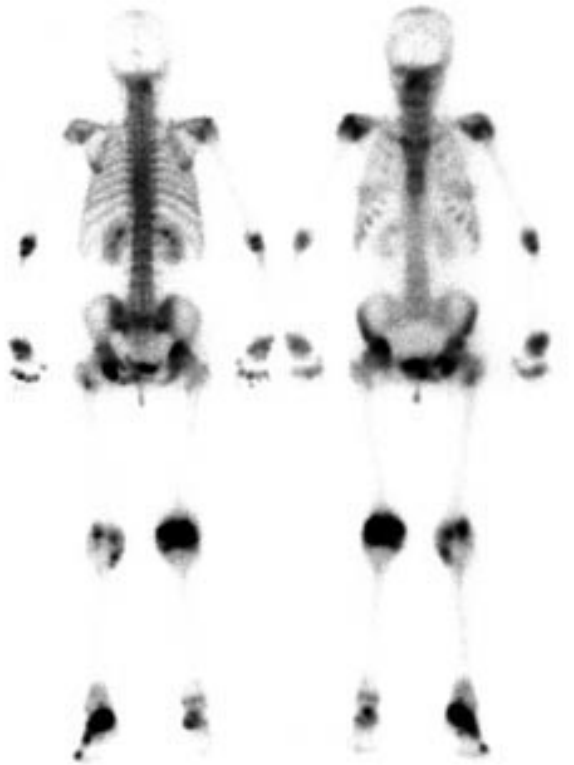

Figure 1 Technetium-99m bone scan (anterior and posterior views, late images) showing multiple zones of enhanced uptake in the superior and inferior right pubic ramus, pubic symphysis, left hip, bilateral femoral condyles, and right calcaneum.

in the lumbar spine, suggesting that the addition of MTX to prednisone may cause more bone loss than would be expected from corticosteroid treatment alone.[7] Recently, Uehara *et al* have shown in vitro that MTX impairs bone formation by inhibiting the differentiation of osteoblast precursors.[8]

In patients with inflammatory arthritis receiving corticosteroids, MTX treatment should be considered as an additional risk factor for stress fractures. As far as we know this is the first reported case of MTX osteopathy in a patient with JIA. Rheumatologists should be aware of this complication as it may be easily confused with synovitis. Involvement of the leg articular or periarticular area should raise diagnostic clinical awareness. A bone scan is particularly useful for the diagnosis.[3]

Authors' affiliations
M Rudler, J Pouchot, S Gentelle, A Grasland, P Vinceneux, Service de Médecine Interne, Hôpital Louis Mourier, Faculté Xavier Bichat, Paris VII, France
F Paycha, Service de Médecine Nucléaire, Hôpital Louis Mourier, Faculté Xavier Bichat, Paris VII, France

Correspondence to: Dr J Pouchot, Service de Médecine Interne, Hôpital Louis Mourier 178, rue des Renouillers, 92700 Colombes, France; Jacques.pouchot@lmr.ap-hop-paris.fr

Accepted 26 November 2002

REFERENCES

1 **Ragab AH**, Frech RS, Vietti TJ. Osteoporotic fractures secondary to methotrexate therapy of acute leukaemia in remission. Cancer 1970;25:580–5.
2 **Maenaut K**, Westhovens R, Dequeker J. Methotrexate osteopathy, does it exist? J Rheumatol 1996;23:2156–9.
3 **Stevens H**, Jacobs JWG, Van Rijk PP, De Klerk JMH. Methotrexate osteopathy demonstrated by technetium-99m HDP bone scintigraphy. Clin Nucl Med 2001;26:389–91.
4 **Wijnands M**, Burgers. Stress fracture in long term methotrexate treatment for psoriatic arthritis. Ann Rheum Dis 2001;60:736–8.
5 **Bologna C**, Sany J, Jorgensen C. Possible role of methotrexate in the distal tibia fractures in a patient with rheumatoid arthritis. Clin Exp Rheumatol 1996;14:343–4.
6 **Zonneveld IM**, Bakker WK, Dijkstra PF, Bos JD, van Soesbergen RM, Dinant HJ. Methotrexate osteopathy in long-term low-dose methotrexate treatment for psoriasis and rheumatoid arthritis. Arch Dermatol 1996;132:184–7.
7 **Buckley LM**, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol 1997;24:1489–94.
8 **Uehara R**, Suzuki Y, Ichikawa Y. Methotrexate (MTX) inhibits osteoblastic differenciation in vitro: possible mechanism of MTX osteopathy. J Rheumatol 2001;28:251–6.

More on anticardiolipin and anti-β_2 glycoprotein I in systemic sclerosis

C M Antonioli, E Danieli, P Airò, R Cattaneo, A Tincani

Ann Rheum Dis 2003;**62**:589–590

Patients with systemic sclerosis (SSc) may have arterial and venous thrombosis and, according to the limited and controversial data available, may have an increased incidence of pregnancy losses.[1] These observations preceded the definition of antiphospholipid syndrome (APS) as the association of thrombosis and pregnancy loss with antiphospholipid antibodies (aPL), and did not focus on patients with SSc. However, the association of thrombosis and aPL, detected as lupus anticoagulant (LAC) and/or anticardiolipin antibodies (aCL), although rare, was described in SSc,[2] supporting the possible existence of a "secondary" APS in SSc.[3]

In view of the fact that most aCL are directed to β_2 glycoprotein I (aβ_2GPI),[4] the possibility that patients with APS may be negative for aCL, but positive for aβ_2GPI,[5] and considering the scarcity of data examining this issue in SSc, we read with great interest the recent study by Schoenroth *et al*,[6] who examined the frequency of aβ_2GPI in SSc. The authors found IgM aβ_2GPI in 2/26 (8%) patients and IgG in none. This finding did not seem to be related to any clinical or laboratory features. In another report, 80 patients with SSc were studied using an enzyme linked immunosorbent assay (ELISA) detecting the complex cardiolipin/β_2GPI. A similar prevalence of aCL/β_2GPI (10% IgG and 6% IgM), was found and a significant correlation between the presence of aCL/β_2GPI IgG and isolated pulmonary hypertension.[7]

Looking retrospectively at our cohort of 115 patients with SSc fulfilling the American College of Rheumatology criteria,

Table 1 Clinical and laboratory features of 18 patients with SSc aCL+ and/or aβ$_2$GPI+

Sex, age, subset of SSc	aβ$_2$GPI*		aCL*		Thromboses	Pregnancy loss	Other clinical and laboratory features	Antithrombotic treatment
	IgG (OD)	IgM (OD)	IgG (GPL)	IgM (MPL)				
F, 37, l	1.68	0.36	67	35	No	No	Overlap SLE, LAC–	Aspirin
F, 55, d	0.38	Neg	Neg	Neg	No	No		Aspirin
F, 57, l	Neg	2.11	Neg	Neg	DVT	2 Miscarriages	Livedo reticularis, LAC–	Warfarin
F, 61, l	Neg	0.84	Neg	Neg	No	No	PBC, LAC–	Aspirin
F, 54, l	Neg	0.66	Neg	Neg	No	1 Miscarriage, 1 intrauterine death		Aspirin
F, 64, l	Neg	0.58	Neg	Neg	No	No	LAC–	Aspirin
M, 65, l	Neg	0.53	13	Neg	Subclavian artery		Non-erosive arthritis, LAC–	Ticlopidine
F, 76, l	Neg	0.43	Neg	15	Recurrent DVT in leg	No		Aspirin
F, 59, l	Neg	0.42	Neg	15	No	No	Pulmonary hypertension	Warfarin + iloprost
F, 63, l	Neg	0.38	Neg	Neg	No	No	Superficial phlebitis	Aspirin
F, 78, l	Neg	0.35	Neg	Neg	No	No		Aspirin
F, 43, l	Neg	0.32	Neg	Neg	No	No		Aspirin
F, 59, l	Neg	0.31	Neg	Neg	No	No	Overlap PM/SLE, LAC–	Aspirin
F, 60, l	Neg	0.30	Neg	Neg	No	No		No
F, 65, l	Neg	Neg	30	Neg	Myocardial infarction	No	Pulmonary hypertension, encephalopathy, LAC+	Warfarin + iloprost
F, 37, d	Neg	Neg	18	Neg	Saphenous vein thrombosis	No	Overlap SLE	Aspirin
F, 54, l	Neg	Neg	20	Neg	No	No		Aspirin
F, 52, d	Neg	Neg	Neg	10.7	No	No		Aspirin

*Normal values: aβ$_2$GPI IgG <0.13, IgM <0.28; aCL IgG <10, IgM <10.
SLE, systemic lupus erythematosus; LAC, lupus anticoagulant; DVT, deep vein thrombosis; PBC, primary biliary cirrhosis; PM, polymyositis.

we found that, where clinically indicated, both aCL and aβ$_2$GPI had been routinely evaluated in 60 patients (four male, 56 female; mean age 57 years; mean disease duration 13 years, range 1–42). These patients were classified, according to Le Roy (1988), as having limited (lSSc; n=48) or diffuse SSc (dSSc; n=12). Twenty seven patients were anticentromere positive and 16 anti-Scl-70+. Anticardiolipin antibodies were evaluated by a routine standardised method,[8] and aβ$_2$GPI as described by Balestrieri *et al*[9]; values higher than the 99th centile of 100 healthy blood donors were regarded as positive.

Positive tests for aCL were found in 8/60 (13%) patients and for aβ$_2$GPI in 14/60 (23%) (table 1). The prevalence of aβ$_2$GPI was higher than in previous studies, probably because we performed the test only where clinically indicated; therefore, the prevalence in patients with SSc overall may differ.

Among 60 patients, eight had a history of documented venous (four) or arterial (four) thromboses: two were aCL+ aβ$_2$GPI+, two aCL+ aβ$_2$GPI–, one aCL– aβ$_2$GPI+, and three aCL– aβ$_2$GPI–; aCL and anamnestic thrombosis were significantly related ($p<0.01$; χ^2 with Yates's correction). Two patients had "primary" (that is, not secondary to lung fibrosis) pulmonary hypertension. One patient was aCL+ aβ$_2$GPI+, whereas the other one was aCL+ and LAC+, but aβ$_2$GPI–; aCL and pulmonary hypertension were significantly related ($p=0.02$). According to the Sapporo criteria[10] three patients had a significant history of pregnancy loss without thromboses: one was aCL– aβ$_2$GPI+, but two were aCL– aβ$_2$GPI–.

In our experience, the presence of aCL in patients with SSc was significantly associated with a history of thrombosis and with pulmonary hypertension. Anti-β$_2$GPI seemed to be less specific, but allowed the identification of a woman with deep vein thrombosis, two miscarriages, and livedo reticularis. Although these events can be related to other thrombophilic conditions, none of these conditions was found in this patient. The association with aβ$_2$GPI suggests that she might be defined as having "aCL–, aβ$_2$GPI + APS" or "equivocal APS".[5]

In conclusion, in patients with SSc and APS related symptoms, the evaluation of aβ$_2$GPI can help to define the clinical picture and the specific treatment required.

Authors' affiliations
C M Antonioli, E Danieli, P Airò, R Cattaneo, A Tincani , Servizio di Reumatologia ed Immunologia Clinica, Spedali Civili, Brescia, Italy

Correspondence to: Dr P Airò, Servizio di Immunologia Clinica, Spedali Civili, 25123 Brescia, Italy; cattaneo@master.cci.unibs.it

Accepted 22 November 2002

REFERENCES

1 **Black CM**, Stevens WM. Pregnancy in patients with rheumatic diseases. Scleroderma. Rheum Dis Clin North Am 1989;15:193–212.
2 **Kane D**, McSweeney F, Swan N, Bresnihan B. Catastrophic antiphospholipid syndrome in primary systemic sclerosis. J Rheumatol 1998;25:810–12.
3 **Cervera R**, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al*. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019–27.
4 **Tincani A**, Balestrieri G, Spatola L, Cinquini M, Meroni PL, Roubey RAS. Anticardiolipin and anti-β$_2$ glycoprotein I in the diagnosis of antiphospholipid syndrome. Clin Exp Rheumatol 1998;16:396–402.
5 **Harris EN**, Pierangeli SS. 'Equivocal' antiphospholipid syndrome. J Autoimmun 2000;15:81–5.
6 **Schoenroth L**, Fritzler M, Lonzetti L, Senecal JL. Antibodies to β$_2$ glycoprotein I and cardiolipin in SSc. Ann Rheum Dis 2002;61:183–4.
7 **Ihn H**, Sato S, Fujimoto M, Kikuchi K, Igarashi A, Soma Y, *et al*. Measurement of anticardiolipin antibodies by ELISA using β$_2$-glycoprotein I (β$_2$-GPI) in systemic sclerosis. Clin Exp Immunol 1996;105:475–9.
8 **Harris E**. The second international anticardiolipin standardization workshops. The Kingston Anti-Phospholipid Antibody Study (KAPS) Group. Am J Clin Pathol 1990;94:476–84.
9 **Balestrieri G**, Tincani A, Spatola L, Allegri F, Prati E, Cattaneo R, *et al* Anti-β$_2$ glycoprotein I: a marker of antiphospholipid syndrome? Lupus 1995;4:122–30.
10 **Wilson W**, Gharavi A, Koike T, Lockshin MD, Branch DW, Piette JC, *et al* International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–11.